# Evaluation of diagnostic accuracy of 75th percentile threshold for a contemporary sensitive and a high-sensitivity cardiac troponin I immunoassays

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We read with interest the article of Meune et al., who recently concluded that decision values below the 99th percentile (e.g., 75th percentile) of troponin I (TnI) and troponin T (TnT) may be associated with a high negative predictive value (NPV), but have a lower accuracy for diagnosing acute myocardial infarction (AMI) [1]. In that study, cardiospecific troponins were measured with Hs-cTnT (Roche Diagnostics) on Elecsys 2010 (Roche Diagnostics), and cTnI-Ultra (Siemens) on ADVIA Centaur immunoassay system (Siemens).

In order to verify whether or not a lower diagnostic cut-off using two other troponin immunoassays may improve the final diagnosis of AMI, we recalculated the 75th percentile on a population of 71 consecutive patients admitted to the emergency department (ED) with chest pain, and for whom a final diagnosis of AMI was ruled out according to the criteria of universal definition of myocardial infarction [2]. At variance with the methods used in the study of Meune et al., we measured TnI with contemporary-sensitive AccuTnI (Beckman Coulter) and prototype high-sensitivity (HS)-AccuTnI (Beckman Coulter) on Access 2 (Beckman Coulter). As previously established, the 99th percentile was 31.5 ng/L (95% CI, 27.7–35.4 ng/L) for AccuTnI and 27.7 ng/L (95% CI, 24.6–30.9 ng/L) for HS-AccuTnI [3], whereas the 75th percentile calculated on our population of ED patients without AMI was 18.0 ng/L (15.6–20.4 ng/L) for AccuTnI and 16.5 ng/mL (95% CI, 14.5–18.5 ng/L) for HS-AccuTnI, respectively.

The validation set consisted in 57 consecutive patients admitted to the ED with suspected AMI, within 3 h from onset of symptoms. Both AccuTnI and HS-AccuTnI were measured at patient admission. Nine out of the fifty seven patients (i.e., 16%) were finally diagnosed with AMI according to criteria of the universal definition of myocardial infarction [2]. The diagnostic performance of the two immunoassays was then compared using both the 99th and 75th cut-offs. The statistical analysis was performed using Analyse-it for Microsoft Excel (Analyse-it Software Ltd, Leeds, UK).

As shown in Table 1, the use of the lower cut-off resulted in increased sensitivity and NPV for either assay, reaching 1.00 in all cases. This diagnostic improvement was only marginally counterbalanced by a decrease of specificity and positive predictive value (PPV), wherein the overall diagnostic accuracy remained virtually unchanged.

In agreement with the study of Meuene et al. [3], the results of our study using two different TnI immunoassays confirm that troponin values at the 75th percentile display a higher sensitivity and NPV than the 99th percentile, regardless of the analytical sensitivity of the method. However, the overall diagnostic accuracy was only marginally affected in our investigation, decreasing from 0.74 to 0.72 for AccuTnI, and remaining unchanged for HS-AccuTnI. This is clearly due to a modest decrease of diagnostic specificity using the lower threshold, which was virtually offset by the remarkably improved sensitivity (Table 1).

An important aspect that prepotently emerges from this investigation, is the challenge of selecting the appropriate diagnostic value according to an analytical and clinical perspective, two aspects that inevitably go hand in hand. The use of the 99th cut-off has been suggested more than a decade ago, when less analytically sensitive methods were commercially available [4], and remained virtually undisputed for long, despite the occurrence of substantial methodological improvements [5]. Since the current contemporary-sensitive and HS methods allow to detect cardiac troponins elevations in a broad array of non-ischemic disorders, revision of criteria used for establishing the diagnostic threshold becomes pivotal [5]. A foremost standpoint is that the reference population should be selected according to the clinical setting where troponin testing is used. Since the majority of troponin testing is performed in the ED, it is undeniable that the selection of a healthy population may be misleading in this setting [6]. It is also noteworthy that a lower cut-off (i.e., the 75th percentile) would yield a much more efficient rule out of patients as demonstrated by the study of Meune et al. and confirmed by our data (in both cases the NPV was 1.00 at $\leq$3 h from onset of chest pain), whereas the slightly lower—or even identical—PPV would not substantially influence the diagnostic efficiency of serial testing,

**Table 1**
Comparison of diagnostic performance of a contemporary-sensitive and high-sensitivity troponin (TnI) immunoassay according to different threshold values.

| | Diagnostic threshold | Sensitivity | Specificity | NPV | PPV | Diagnostic accuracy |
|---|---|---|---|---|---|---|
| **AccuTnI 99th percentile** | 31.5 ng/L | 0.78 (95% CI, 0.40–0.97) | 0.73 (95% CI, 0.58–0.85) | 0.95 (95% CI, 0.82–0.99) | 0.35 (95% CI, 0.15–0.59) | 0.74 |
| **AccuTnI 75th percentile** | 18.0 ng/L | 1.00 (95% CI, 0.66–1.00) | 0.67 (95% CI, 0.52–0.80) | 1.00 (95% CI, 0.89–1.00) | 0.34 (95% CI, 0.13–0.57) | 0.72 |
| **HS-AccuTnI 99th percentile** | 27.7 ng/L | 0.78 (95% CI, 0.40–0.97) | 0.69 (95% CI, 0.54–0.81) | 0.94 (95% CI, 0.81–0.99) | 0.32 (95% CI, 0.14–0.55) | 0.70 |
| **HS-AccuTnI 75th percentile** | 16.5 ng/L | 1.00 (95% CI, 0.66–1.00) | 0.65 (95% CI, 0.49–0.78) | 1.00 (95% CI, 0.89–1.00) | 0.32 (95% CI, 0.12–0.52) | 0.70 |

NPV, Negative Predictive Value; PPV; Positive Predictive Value.

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which can be substantially shortened using the latest generation methods [7]. According to this evidence, we suggest that further investigations should be planned to verify whether troponin values below the 99th percentile at presentation may represent a further advancement in the challenging diagnostics of AMI.

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# Magnetocardiographic demonstration of complex ventricular preexcitation resulting in ablation failure

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The Wolff–Parkinson–White (WPW) syndrome affects 1 to 3 persons per 1000. Catheter ablation (CA) is nowadays proposed as the preferred therapy (with success in more than 90% of cases) and ECG is the most used non-invasive method for classification and to choose the interventional approach [1,2]. However, in some cases, difficulties might arise during the electrophysiologic study (EP), due to unexpected complex (or multiple) ventricular preexcitation (VP), especially paraseptal [3]. Therefore several non-invasive methods have been proposed to improve preoperative localization and to minimize the risk of failure and prolonged exposure to radiation [4,5].

Magnetocardiographic mapping (MCG) is an alternative, not yet familiar to clinicians, although its diagnostic value been recently underlined [6,7]. Compared with other non-invasive methods, MCG provides better accuracy and unrivaled three-dimensional (3D) electroanatomical integration and imaging (EAI) to localize ventricular preexcitation [2,8].

Here we report two WPW patients, come to our observation after unsuccessful ablation attempted in other institutions. In both, pre-interventional ECG classification of VP was uncertain. Post-interventional MCG provided 3D imaging of complex VP, which, if available before catheterization, could have probably avoided the ablation failures.

Unshielded MCG was performed with a 36-channel system *(CARDIOMAG IMAGING INC., Schenectady, USA)* (sensitivity 20 ft/√Hz at 1 Hz), recording the *z*-component of magnetic field, from the anterior chest wall, with 24 bits A/D conversion, 1 kHz sampling frequency.[6,8] For 3D localization of preexcitation through the solution of the inverse problem the Equivalent Current Dipole (ECD), Effective Magnetic Dipole (EMD) and Currents Reconstruction (CR) models were used [2,6,8,9]. The intrinsic MCG accuracy for 3D localization of cardiac sources had been previously evaluated with the amagnetic catheter technique [10]. Invasive endocardial mappings, performed with conventional catheters (patient 1) and with the CARTO® system (patient 2), were available from previous ablations. Both patients underwent MCG after written informed consent. Each MCG session lasted 5 min.

Patient 1 (Fig. 1), 20-year-old, with left VP. According to ECG algorithms [1,2] preoperative classification of VP was uncertain (Fig. 1a), but preoperatively classified as left posteroseptal. Interestingly only a left sided VP was predictable on the basis of the 12-lead ECG, confirmed during the invasive EPS (Fig. 1b) and radiofrequency (RF) ablation was initially successful (Fig. 1c). However three months later, a relapse of VP was observed. ECG was unchanged (as in Fig. 1a). MCG, carried out to attempt a more appropriate classification and localization of the accessory pathway (AP), showed atypical magnetic field distribution, during the first 40 ms of the delta wave (Fig. 1d), with changes in the direction of the depolarisation of the posteroseptal area (from right-to-left until the 25th ms, and from left-to right thereafter). Such pattern of complex activation of the posteroseptal area is suggestive of double and/or oblique APs. Multimodal EAI of MCG localization, into a realistic 3D model of the patient's heart (Fig. 1e) and with cardiac MRI images (Fig. 1f), confirmed double VP, located at the right side of the interventricular septum and at the left posteroseptal area (Fig. 1e, f and g). Based on MCG information the double VP was successfully ablated with a second intervention.

Patient 2 (Fig. 2), 22 years old, seen after two unsuccessful CAs performed elsewhere. Classification of VP with ECG algorithms had a certain degree of ambiguity (Fig. 2a). According to ECG, the most probable location of the AP was anteroseptal and a first electroanatomical CARTO® map (Fig. 2b) had apparently confirmed a right

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